REMARKS

Applicants acknowledge receipt of the Final Office Action mailed July 7, 2003 (Paper No. 10). Claim 16, previously added in a prior amendment, is currently amended to add the adjective "purified", which was overlooked in the previous amendment. Reconsideration and withdrawal of the present rejections in view of the comments presented herein are respectfully requested.

Restriction of Claims 21-25 is not proper

Claims 21-25 were submitted as new claims in the amendment that accompanied the response to the previous Office Action, Paper No. 8. Claims 21-25 are directed toward methods for treating polycystic ovary syndrome (PCOS) comprising the administration of a synthetic chromium complex. The Examiner has stated that Claims 21-25 represent a distinct invention from the other pending claims and thus their restriction for examination purposes is proper. Applicants respectfully disagree.

If two or more independent and distinct inventions are claimed in one application, the Director may require the application to be restricted to one of the inventions. M.P.E.P. §802. The M.P.E.P. provides guidance as to the meaning of the terms "independent" and "distinct". "The term 'Independent" (i.e. not dependent) means that there is no disclosed relationship between the two or more subjects disclosed, that is, they are unconnected in design, operation or effect". Furthermore: "(t)he term 'distinct', means that two or more subjects as disclosed are related, for example, as combination and part (subcombination) thereof, process and apparatus for its practice, process and product made, etc., but are capable of separate manufacture, use, or sale as claimed, AND ARE PATENTABLE (novel and unobvious) OVER EACH OTHER" (emphasis in original). M.P.E.P. §803.

In the response to the previous Office Action, Claims 16-25 were added to the claims set. Claims 16 and 21 are independent claims, bringing the total number of independent claims in the amended claim set to three. Claims 17-20 are dependent on Claim 16 and Claims 22-25 are dependent on Claim 21. Claims 16 and 21 are the same as the original independent Claim 1 except for the definition of the form of chromium being administered to the individual. Claims 16 and 21 provide narrower definitions of the invention, Claim 16 being limited to compositions

consisting essentially of a purified chromium-containing compound and Claim 21 being limited to compositions comprising a synthetic chromium complex.

The Examiner asserts that the restriction of Claims 21-25 is proper because the method is drawn to the treatment of PCOS comprising administration of a synthetic chromium complex, whereas the method of Claim 1 is drawn to the treatment of PCOS comprising administration of a chromium compound. The Examiner asserts that:

1. the methods are independent since they are not disclosed as capable of use together;
2. the methods have different modes of operation;
3. the methods have different functions; and/or
4. the methods have different effects.

Applicants disagree with each of these statements.

A synthetic chromium complex would necessarily fall underneath the definition of a chromium compound. Thus, it is a species or subgenus of a previously claimed genus, and is intermediate in scope between two previously examined claim terms, i.e. "chromium containing compound" (Claim 1) and "chromium picolinate" (Claim 2). The specification discloses both the necessity of chromium in the diet, the inadequacy of supplementing with inorganic chromium and the synthesis of organic forms of chromium for use as supplements (pages 7-9). In this way the specification discloses the relationship between chromium compounds (such as those found in natural organic sources) and synthetic chromium complexes and shows how they are connected in design, operation and effect. Hence, the two claims do not qualify as independent, according to the M.P.E.P. The Examiner states that the methods are independent since they are not disclosed as capable of use together, but in reality the use of synthetic chromium picolinate or nicotinate, manufactured with methods found in the disclosed patent references, in the method of Claim 21 would completely fall within the claimed subject matter of Claim 1. Thus, the inventions are not independent. The methods of Claim 21 are not capable of separate use as claimed, since a compound consisting of a synthetic chromium complex would also qualify as a chromium compound. Thus, Claims 1 and 21 are not distinct as defined in the M.P.E.P.

The method of Claim 21 is therefore not independent nor distinct from the method of Claim 1 in a restriction context. Restriction of Claims 21-25 is improper. Applicants respectfully request the examination of Claims 21-25 as part of the entire amended claim set.

Claims 16-20 point out and distinctly claim subject matter under 35 U.S.C. § 112, second paragraph:

In the current Final Office Action, Claims 16-20 have been rejected as indefinite under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner contends that the meaning of the term 'consisting essentially of' is unclear and therefore the claim language was interpreted as if the word 'comprising' had been used, in accordance with Section 2111.03 of the M.P.E.P.

The second paragraph of 35 U.S.C. § 112 contains requirements for the claims of a patent. As stated in M.P.E.P. 2171, there are two separate requirements set forth in the second paragraph of this statute:

"(A) the claims must set forth the subject matter that applicants regard as their invention; and

(B) the claims must particularly point out and distinctly define the meters and bounds of the subject matter that will be protected by the patent grant."

The Examiner asserts that the phrase 'consisting essentially of' is indefinite because, in the Examiner's opinion, the metes and bounds of the phrase are not clearly understood. The Examiner insists that the it is confusing since the specification and the claims teach that other pharmacologically active ingredients may be added to the composition for treating PCOS. Thus, the Examiner's rejection of the claims as indefinite under 35 U.S.C. § 112, second paragraph, is due to an alleged lack of clear meaning for the term "consisting essentially of."

"Consisting essentially of" has a well understood meaning in the law and needs no definition in the specification. According to M.P.E.P. 2111.03, the transitional phrase "consisting essentially of" limits the scope of a claim to the specified material or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention (emphasis in original). *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). Further down in the same section, the M.P.E.P. addresses a relatively rare situation involving inadequate disclosure, and states that "absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, 'consisting essentially of' will be construed as equivalent to 'comprising'". *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355.

Just as with other transitional phrases, 'consisting essentially of' has a legally-recognized meaning and needs no definition. In Section 2111.03, the M.P.E.P. delivers a distinct and concrete definition of the meaning of the term 'consisting essentially of'. There is no requirement in any section of the M.P.E.P. for the Applicant to define what is meant by this term. As for the Examiner's interpretation of the meaning of the term 'consisting essentially of', the M.P.E.P. states that the term 'consisting essentially of' will be construed to mean 'comprising' only in those rare cases where there is no "clear indication in the specification or claims of what the basic and novel characteristic [of the invention] actually are." Thus, if there is a clear indication in the specification or claims what the basic and novel characteristics actually are, then there is no justification for interpreting the term 'consisting essentially of' as having the same meaning as 'comprising'.

From both the specification and the claims, it is clear what the basic and novel characteristics of the invention are. First, the title of the application states that compositions of the invention will contain certain compounds, namely "chromium complexes". From this alone, the reader understands that a composition of the invention will have the basic characteristics imparted by a chromium complex. Second, the section entitled "Detailed Description of the Preferred Embodiment" discusses chromium compounds and various formulations for these compounds. The beneficial effects of dietary chromium on PCOS are discussed in detail.

Once this topic is introduced, the specification is clear regarding the purposes of including additional substances, including the chelating agents listed in Claims 18 and 19. The purpose clearly described in the specification for the inclusion, in some embodiments of the invention, of chelating agents is to create coordinated forms of chromium that are directly available for absorption without competition from other metals (pages 7-9). As the specification explains clearly, the purpose for the chelating agents is to enhance the absorption of chromium. By enhancing the absorption of chromium into the body from the lumen of the digestive tract, more chromium from the oral formulation becomes bioavailable and able to contribute the reduction of PCOS symptoms. These added ingredients are beneficial, but not essential. They simply allow the ingredients recited in the independent claims to have more of their original activity. Thus, the supporting role of these additional ingredients is clear, and the dependent claims that recite the combinations that include such additional ingredients are not indefinite.

As stated above, the M.P.E.P. defines "consisting essentially of" as limiting the scope of a claim to the specified material or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. As discussed in the specification, the core medicinal effect of the invention is caused by chromium compounds. Conventional excipients do not materially change that effect. The added ingredients do not themselves provide a substitute or competitive pharmacological activity; rather they simply permit chromium to better fulfill its pharmacological purpose. The specification defines what the basic and novel characteristics of the invention are and the dependent claims stay well within the defined metes and bounds of the term "consisting essentially of", as the term appears in the independent claim and as it is defined in the M.P.E.P., Section 2111.03. Applicants respectfully request that the claims be interpreted using the term "consisting essentially of" and that the rejection of Claims 16-20 based on 35 U.S.C. § 112, second paragraph, be withdrawn.

Claims 1-20 are not unpatentable over de la Harpe et al. (U.S. Pat. No. 5,980,905) in view of Ostlund et al. (U.S. Pat. No. 5,550,166)

In the previous Office Action, the Examiner rejected Claims 1-15 as being unpatentable over de la Harpe *et al.* (U.S. Pat. No. 5,980,905) in view of Ostlund *et al.* (U.S. Pat. No. 5,550,166). Applicants argued that de la Harpe discloses the treatment of diabetes symptoms but not of insulin resistance and that the prior art does not fulfill the requirements for a *prima facie* case of obviousness. The Examiner did not accept the arguments. In the Final Office Action, Claims 1-15 remain rejected and Claims 16-20 are newly rejected under 35 U.S.C. §103(a) as being unpatentable due to *prima facie* obviousness over de la Harpe *et al.* ('905) in view of Ostlund *et al.* ('166).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. §2143.

The '166 reference discloses the use of a carbohydrate compound isolated from plants, pinitol, to treat conditions associated with insulin resistance (IR). The patent discloses that some of the actions of insulin may be mediated through inositol phosphoglycan molecules released

from cell membranes in response to insulin (column 2, line 3) and suggests that augmenting the release of these molecules is one way to improve insulin sensitivity. The patent also discloses that D-chiro-inositol was found to be the sole or predominant inositol in some of the inositol phosphoglycans analyzed and that diabetics have reduced amounts of this substance in their tissues and fluids. The patent states that this has provided others with a rationale for exploring the use of D-chiro-inositol for treatment of diabetes. According to the patent, pinitol is a methyl-ester of D-chiro-inositol and is readily hydrolized into D-chiro-inositol. The patent reveals that administration with pinitol is effective for the treatment of type II diabetes. Thus, consumption of pinitol by an individual leads to greater amounts of a signaling molecule that is normally released in response to insulin exposure in the individual, which presumably leads to greater glucose uptake by cells, lower blood glucose and amelioration of diabetes symptoms.

The '905 reference discloses and claims formulations of chromium with other ingredients and methods for reducing serum blood glucose, reducing hyperglycemia, stablizing blood glucose levels, increasing lean body mass, reducing body fat and reducing high levels of blood serum lipids by administering a chromium supplement. The patent discloses that dietary chromium supplementation has been observed to lead to numerous physiological changes, some of which are opposed to symptoms of diabetes, and that chromium functions as a co-factor for insulin.

In the Final Office Action, the Examiner states that '905 clearly taught that chromium supplementation was linked to improvements in insulin binding. The Examiner also states that '905 taught that chromium acts as a co-factor for insulin, binds to the insulin receptor and potentiates many of its functions. The Examiner then concludes that these statements, taken together, mean that chromium acts in alleviating insulin resistance. Thus, it would have been obvious to one with skill in the art to take the insulin resistance-alleviating chromium of '905 and use it in the manner of Ostlund, to treat conditions related to insulin resistance. Applicants respectfully disagree.

Insulin resistance (IR) is defined as the diminished ability of cells to respond to the action of insulin in transporting glucose (sugar) from the bloodstream into muscle and other tissues (see http://www.medterms.com/script/main/art.asp?articlekey=18822). The response of blood glucose levels to insulin, either administered to an individual or released by the body in response to food ingestion, can be measured. When that response is lower than expected, the body is said

to be resistant to insulin. IR, alternatively defined as the "impairment of normal biologic responses to insulin", can have multiple causes, including "abnormalities in the beta-cell products, binding of insulin to antagonists such as anti-insulin antibodies, defects in or reduced numbers of receptors, or defects in the insulin action cascade in the target cell" (see http://www.mercksource.com/pp/us/cns/cns_hl_dorlands.jspzQzpgzEzzSzppdocszSzuszSzcommonzSzdorlandszSzdorlandzSzdmd_r_09zPzhtm#1095787). Diabetes mellitus, however, is a generic term relating to a condition that is characterized by hyperglycemia, i.e. abnormally high levels of glucose (blood sugar) in the blood (http://www.wikipedia.org/wiki/Diabetes_mellitus). Thus it is clear that while IR may be a sign of a pre-diabetic condition and that a person diagnosed with diabetes may display symptoms of IR, the two conditions are not one and the same and certainly do not need to co-exist in any one patient.

The '905 patent specifically states:

> "Dietary supplementation of chromium to normal individuals has been reported to lead to improvements in glucose tolerance, serum lipid concentrations, including high-density lipoprotein cholesterol, insulin and insulin binding" (column 1, lines 45 to 48).

The '905 patent also states:

> "Chromium acts as a co-factor for insulin. It binds to the insulin receptor and potentiates many, and perhaps all, of its functions" (column 1, lines 54-55).

The Examiner has concluded from combining the two statements above that "chromium acts in alleviating insulin resistance" (page 5 of Paper No. 10). This conclusion is erroneous. The Examiner appears to have concluded from the first statement above that because the supplementation of chromium leads to numerous physiologically detectable changes in normal individuals, these changes are necessarily related to one another. However, no relationship is discussed by the reference between any of the effects produced by chromium supplementation. Improvements in insulin binding may be causing improvements in serum lipid concentrations, or vice versa, or there may be no cause and effect relationship between improvements. It simply is not known from the information in the reference. The only information gained from the statement is that chromium supplementation in normal individuals leads to a plethora of effects, which may or may not be important or related to one another. Second, the first statement above concerns normal individuals, i.e. not individuals with insulin resistance or diabetes. One cannot

draw conclusions regarding IR on the basis of experments or tests performed on normal individuals. In other words, just because chromium supplementation causes increased glucose tolerance in normal individuals does not predict what effect it would have in individuals with IR, a pre-diabetic condition or diabetes. Finally, the hallmark of IR is the response of blood glucose levels to the release of insulin. No information in the above two statements or anywhere else in either of the two references shows or suggests a cause-and-effect relationship between chromium binding to insulin receptors and glucose tolerance. Chromium supplementation may lead to chromium binding to insulin, its receptor or any other protein and may lead to increased glucose tolerance, but the coincidence of these or any other effects is not proof of a causal relationship. Thus, the Examiner's conclusion that chromium binding to insulin receptors can alleviate IR is based on hindsight and is not taught by the references.

The '166 reference discloses the treatment of PCOS with a carbohydrate that treats the symptoms of IR. However, there is no evidence provided anywhere in the references of a link between chromium supplementation and the alleviation of IR. Even if such a link existed, the prior art would not provide a definate connection between chromium binding to the insulin receptor and the treatment of PCOS as disclosed in '166, since the treatment of PCOS disclosed in '166 does not involve interactions with insulin or its receptor. The treatment of PCOS disclosed in '166 involves the mimicking of the signal produced in cells in response to insulin exposure. The signal is produced without the activity of insulin. Pinitol does not bind to, interact or potentiate insulin, its receptor or their level of activity. Evidence of the efficacy of an insulin signal mimic to treat PCOS does not necessarily mean that an insulin receptor binding agent such as chromium would also be effective. The two treatments act on different molecules in a different manner through different mechanisms. Hence, the prior art neither provides a link between chromium supplementation and alleviation of IR, nor provides evidence supporting the relevance of such a link. Thus, there is no motivation or suggestion to modify or combine the references to use chromium supplementation for the treatment of conditions associated with IR. Without such a motivation or suggestion, the prior art fails to provide the first criteria for a *prima facie* case of obviousness.

The Instant specification states that women with PCOS are at increased risk for developing impaired glucose tolerance (IGT) and type II diabetes (paragraph 15, page 4). Thus, while some women diagnosed with PCOS will go on to develop IGT and type II diabetes, others

will not. The prior art discloses the utility of chromium supplementation to treat the symptoms of diabetes. However, nothing in the prior art or the specification suggests that diabetes is causing PCOS or that there is even a causal relationship between the two conditions. PCOS and diabetes could both be effects of a third, undetermined cause. While PCOS has been linked to IR in the '166 reference, the prior art does not present evidence that would have allowed one with skill in the art to conclude that chromium supplementation would alleviate IR, nor does the prior art provide evidence that any ability of chromium to alleviate IR would be effective against PCOS. Thus, the prior art does not provide a reasonable expectation of the success of treating PCOS with chromium supplementation. Hence, the prior art fails to provide the second criteria of *prima facie* obviousness.

The '166 patent discloses and claims compositions with pinitol or a derivative useful in treating conditions of insulin resistance. The '166 patent also claims methods of treating conditions of insulin resistance comprising administering an effective amount of pinitol or a derivative. The present invention relates to a method of treating PCOS comprising identifying a patient with PCOS and adminstering an effective dose of a chromium-containing composition. The '166 reference does not teach the step of identifying a patient with PCOS and does not teach the administration of chromium. The '905 reference teaches compositions with chromium and a method of treating various syndromes with these compositions, but, as discussed above, does not teach the treatment of IR with chromium. The '905 reference is silent with regard to PCOS. Thus, combination of the references fails to teach all of the limitations of the claims. Hence, the prior art fails to provide the third criteria for a *prima facie* case of obviousness.

With the above arguments, Applicants have demonstrated the failure of the cited prior art to establish any of the three required criteria for *prima facie* obviousness. Applicants therefore respectfully request the elimination of the rejections of Claims 1-20 under 35 U.S.C. §103(a) over de la Harpe et al. in view of Ostlund et al.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Final Office Action. Accordingly, the arguments in support of the patentability of the pending claim set are presented above. In light of the above remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: 9-5-02

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